Remarks

Courtesies extended to Applicants' representative in the personal interview held on February 4, 2004, are acknowledged with appreciation.

In accordance with the present invention, there are provided chimeric proteins comprising a covalent fusion of at least two functional protein units, wherein each functional protein unit comprises the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily (see Figure A schematic below showing 2 functional protein units, each containing a dimerization domain, which are covalently fused into a single polypeptide molecule).

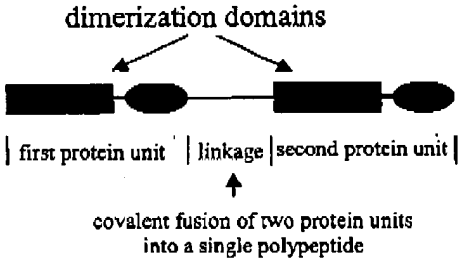

Figure A – exemplary chimeric fusion protein construct

The present claims are directed to a chimeric protein comprising at least two functional protein units. Each of these functional protein units comprises at least the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily. The functional protein units form a functional entity, such that the resultant chimeric protein is biologically active. All that is required by the present claims is to make the chimeric protein comprising a fusion of at least two functional protein units (comprising the desired functional domains as claimed) using standard molecular biological techniques for making recombinant proteins, and to test whether the resulting protein exhibits one of the clearly identified biological functions using functional assays, such as those taught in the working examples of the specification.

Claims 1-11 and 13-22 remain pending pursuant to this communication. The present status of all claims in the application is provided in the listing of claims presented herein beginning on page 2.

The rejection of claims 1-11 and 13-22 under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to reasonably provide enablement for the chimeric proteins as claimed, is respectfully traversed.

It is respectfully submitted that this rejection, in substantially the same form, has previously been asserted, and **withdrawn**. Specifically, in the Office Action mailed November 19, 2002, the Examiner states that the "rejection of claims 1-11, 13-22 under 35 U.S.C. 112, first paragraph has been obviated by Applicant's amendment, and is thus withdrawn" (see Office Action, Paper No. 15, at page 2, lines 7-8). The language of claim 1 at the time of withdrawal of the enablement rejection and the currently pending claim 1 is compared below:

Claim 1 – November 19, 2002	Claim 1 – currently pending
1. A chimeric protein comprising:	1. A chimeric protein comprising:
a fusion of at least two functional protein units, wherein each functional protein unit comprises the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily, and	a fusion of at least two functional protein units, wherein each functional protein unit comprises the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily;
an optional linker interposed therebetween,	wherein said at least two functional protein units are covalently fused into a single polypeptide molecule by (i) fusion of said protein units, or (ii) use of a linker interposed between said protein units; and
wherein the at least two protein units form a functional entity,	
such that said chimeric protein is capable of at least one function selected from the group consisting of DNA binding, ligand binding, transactivation and dimerization.	wherein said chimeric protein is capable of at least one function selected from the group consisting of DNA binding, ligand binding, transactivation and dimerization.

As can be seen from the above comparison, only the linker feature of claim 1 has been amended since the enablement rejection of claim 1 was withdrawn by the Examiner. Therefore, enablement of the functional protein units that are fused to create the invention chimeric protein has already been acknowledged.

To the extent that there may be any new, yet unasserted, basis for repeating what appears to be the same enablement rejection, Applicants respectfully submit that they have met the standard for enablement of the present invention. The standard for determining enablement is whether the specification as filed provides sufficient information so as to permit one skilled in the art to make and use the claimed invention (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988)). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation would proceed" (*In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

According to this test of enablement, Applicants have provided more than a reasonable amount of guidance with respect to any experimentation required to carry out the present invention. With respect to the functional protein units, the specification teaches domains that can be used to form each functional protein unit and presents exemplary domains for use in the practice of the invention. For example, DNA binding domains are described at page 16, line 8, through page 18, line 13; ligand binding domains are described at page 14, line 26, through page 15, line 26; activation domains are described at page 18, line 14, through page 19, line 2; and dimerization domains are described at page 10, line 27, through page 11, line 18. One of skill in the art, in light of the teachings of the specification and knowledge in the art, could readily determine appropriate domains to assemble in the construction of a chimeric protein in order to achieve one or more biological functions. Moreover, Example 1 teaches the complete design and construction of exemplary chimeric fusion constructs.

Moreover, the Examiner has acknowledged that the specification is enabling for a chimeric protein "comprising a fusion of EcR-USP/RXR into a functional dimer" (see Office Action mailed December 24, 2003, at page 2, lines 18-19) (*i.e.*, the working examples of the present application). Again, it is respectfully submitted that the working examples employ

receptor members that are highly representative of the entire superfamily. Thus, additional examples with further superfamily members are clearly not necessary. Indeed, given the well characterized nature of all members of the nuclear receptor superfamily, additional examples with further superfamily members would merely be superfluous. Therefore, the claims should not be limited to just the working examples provided.

Applicants respectfully disagree with the Examiner's assertion that "detailed information regarding the structural and functional requirements of the polypeptide are lacking" (see Office Action mailed December 24, 2003, at page 4, lines 3-4). As previously noted in Applicants' Responses of record, members of the superfamily are commonly characterized by the presence of five domains, one of which is the required dimerization domain (see, for example, specification at page 11, lines 3-7); and significant homologies exist in domains within members of the superfamily, which have been extensively studied in the art. The receptors used in the examples provided (*i.e.*, the ecdysone, Usp or retinoid X receptors) are highly representative of the superfamily. One of skill in the art would clearly appreciate the interchangeability of domains of different members of the superfamily to create novel functional chimeric proteins.

Furthermore, the reference cited by the Examiner, Aranda and Pascual, *Physiol. Rev.* 81:1269-1304, 2001 (hereinafter referred to as "Aranda"), in fact supports enablement of the full scope of the present claims. Aranda states "[l]ike other transcriptional regulators, nuclear receptor exhibit a modular structure with different regions corresponding to **autonomous functional domains that can be interchanged between related receptors without loss of function**" (emphasis added, see Aranda at page 1271, A. Domain Structure). The present claims only require that at least two such functional units are combined to form a chimeric protein that has at least one function selected from the group consisting of DNA binding, ligand binding , transactivation and dimerization. One of skill in the art could readily identify putative functional domains to utilize in the preparation of such constructs to achieve a desired function. The facts that "the exact biochemical mechanisms by which these receptors stimulate transcription are still unclear" or that "there are functional differences with the superfamily" (see Office Action mailed

December 24, 2003, at page 3, lines 10-12, and 14-15) are simply irrelevant to enablement of the present claims.

Moreover, any experimentation required to create such chimeric constructs is merely routine, and could be readily conducted by one of ordinary skill in the art. A considerable amount of experimentation is permissible, and the level of experimentation required to make and use the chimeric proteins of the present invention clearly does not amount to undue experimentation.

For all of the reasons set forth above, it is respectfully submitted that the present claims as amended are fully enabled as required by 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of this rejection of claims 1-11 and 13-22 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

The rejection of claims 1-11 and 13-22 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed had possession of the claimed invention, is respectfully traversed. Contrary to the Examiner's incorrect assertion that "no common structural attributes identify the members of the genus" (*i.e.*, the steroid/thyroid hormone nuclear receptor superfamily; see Office Action mailed December 24, 2003, at page 5, lines 18-19), this superfamily contains a remarkably uniform domain structure that was well-known in the art at the time of filing of the present application.

Furthermore, as discussed above, the specification teaches domains that can be used to form each functional protein unit and presents exemplary domains for use in the practice of the invention. Specifically, DNA binding domains are described at page 16, line 8, through page 18, line 13; ligand binding domains are described at page 14, line 26, through page 15, line 26; activation domains are described at page 18, line 14, through page 19, line 2; and dimerization

domains are described at page 10, line 27, through page 11, line 18. Clearly, the specification provides more than ample description of the conserved regions of the members of the receptor superfamily, in addition to the knowledge of one of skill in the art.

Therefore, one of skill in the art would have no reason to doubt that Applicants were in possession of the present invention at the time of filing. Accordingly, reconsideration and withdrawal of this rejection of claims 1-11 and 13-22 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Conclusion

In view of the above remarks, prompt and favorable action on all claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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